UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/602,838	06/24/2003	Birthe Lykkegaard Hansen	6423.404-US	9325

23650 7590 05/31/2007

NOVO NORDISK, INC.
PATENT DEPARTMENT
100 COLLEGE ROAD WEST
PRINCETON, NJ 08540

EXAMINER	
HA, JULIE	

ART UNIT	PAPER NUMBER
1654	

NOTIFICATION DATE	DELIVERY MODE
05/31/2007	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

nnipatent@novonordisk.com
trab@novonordisk.com
rhaj@novonordisk.com

Office Action Summary	Application No.	Applicant(s)	
	10/602,838	HANSEN ET AL.	
	Examiner	Art Unit	
	Julie Ha	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *April 09, 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19,21-26 and 29-31* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-19,21-26 and 29-31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on April 09, 2007 has been entered. Request for Continued Examination (RCE) filed on April 09, 2007 is acknowledged. Claims 20, 27-28 and 32-37 were cancelled on the Amendment after final filed on February 12, 2007. Claims 1-19 and 21-26 and 29-31 are examined on the merits in this office action.

Rejection-35 U.S.C. 112, 2nd

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 1-19, 21-26 and 29-31 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

3. The base claim 1 recites that factor VII polypeptide "retains at least 50% of its biological activity". This recitation is unclear, since it is unclear if the factor VII polypeptide itself is retaining the activity without components (ii) and (iii) or components (ii) and (iii) are required to retain 50% of its biological activity.

Rejection-35 U.S.C. 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5. Claims 1-7, 9-16, 21-23, 25-26 and 29-31 are rejected under 35 U.S.C. 102(b) as being anticipated by The Medicine Catalogue (Laegemiddel Kataloget), of record. Note that the date of public availability of this reference has been determined to be July 19, 2000, thus qualifying the reference as prior art under 102(b).

6. The instant claims are drawn to a liquid, aqueous composition comprising (i) a factor VII polypeptide in a concentration of from about 0.1 mg/ml to about 10 mg/ml, (ii) an agent suitable for keeping pH in the range of from about 5.5 to about 7.0 is selected from the group consisting of acids and salts in a concentration of about 1 mM to about 50 mM, (iii) an agent selected from a calcium salt, a magnesium salt, or a mixture thereof, wherein the concentration of (iii) is at least 20 mM, (iv) an ionic strength modifying agent, sodium chloride (at least about 5 mM), (v) a tonicity modifying agent in a concentration from 1 mM to 500 mM, (vi) a non-ionic surfactant is a polysorbate or a poloxamer or a polyethylene alkyl ether, further comprising factor VII polypeptide is stable for at least 6 months at 2-8°C and recombinant human factor VIIa.

7. The Medicine Catalogue discloses a composition with recombinant coagulation factor VIIa, with 105 mg calcium chloride, 1.3 mg glycylglycine, 30 mg mannitol, 3.0 mg sodium chloride and 0.1 mg polysorbate per 80 ml, wherein the composition has a pH of

5.4 to 6.0 (see Dispensed in the form of). When a simple calculation is performed for $CaCl_2$ concentration using 105 mg and molecular weight of 111 g/mol and dissolving in 2, 4 and 8mls of sterile water, the $CaCl_2$ concentrations are 118 mM, 236 mM and 473 mM, respectively for 8, 4 and 2mls. For sodium chloride (MW 59 g/mol) and using 3 mg and dissolving in 2, 4 and 8mls of sterile water, the sodium chloride concentrations are 6, 12 and 24 mM, respectively for 8, 4 and 2mls (see Suggested dosage). This meets the limitation of at least 20 mM of calcium salt of claim 1 (iii) and at least 5 mM of sodium chloride. Therefore, this reads on claim 1-7, 9-16, 21-23 and 26. With regards to factor VII polypeptide stable for at least 6 months at 2-8C, the stability of the composition is a property of its components, accordingly, since the prior art composition has the same components as the composition of instant claims, the stability will be the same. Thus, this reads on claim 25. The Medicine Catalogue further teaches that factor VII polypeptide concentration is 0.6 mg/ml when a calculation is performed using the amount of recombinant coagulation factor (1.2 mg, 2.4 mg or 4.8 mg) is dissolved in 2 ml, 4 ml, and 8 ml of sterile water (see Suggested dosage under "Preparation of injection fluid"). This reads on claim 29. Furthermore, The Medicine Catalogue teaches that the preparations are dissolved in varying amounts of sterile water, and that they are administered by a bolus injection (see Suggested dosage). This reads on claims 30-31. Additionally, since different amounts of sterile water are used to reconstitute the composition while the mass of the excipients does not change, the concentrations of the excipients will be commensurate with instant claims. For example, 30 mg of mannitol (MW 182.17 g/mol) used in The Medicine Catalogue, which meets the limitation of claim

11 is found to be 82 mM for 2ml, 41 mM for 4ml and 21 mM for 8mls of sterile water, meeting the limitations of claims 12-13. It is noted that claims 1, 5-6, 19, 21-23 and 29-31 have been rejected over the prior art, even though the reference does not disclose exact pH range and exact amount (range) as claimed. However, the claims utilize the term "about" when discussing the pH and the amount. The term "about" allows for some tolerance in the ranges disclosed. In In re Ayers, the Federal Circuit held that "at least about 10%" was anticipated by a reference that disclosed "about 8%" because the term "about" allowed for some tolerance. In re Ayers, 154 F.2d 182, 185 (Fed. Cir. 1946). Similarly, in Johnson and Johnson v. W.L. Gore & Associates, Inc., the Court allowed for "about 1.2" to be inclusive of 1.0. See Johnson and Johnson v. W.L. Gore & Associates, Inc., 436 F.Supp. 704, 728-729 (Fed. Cir. 1977). Although about has never been confined to specific percentage of variability, the Johnson and Johnson decision at least implies that 16% variability is permissible when "about" is used (1.0/1.2 = ~16.6% variability). Thus, the term "about" implicitly discloses some variability even though the specification may not literally cite this variability. Therefore, The Medicine Catalogue meets the limitations of claims 1-7, 9-16, 21-23, 25-26 and 29-31.

8. Claims 1-7, 9-19, 21-26, 29-31 are rejected under 35 U.S.C. 102(b) as being anticipated by Johannessen et al (WO 01/82943).

9. The instant claims are drawn to a liquid, aqueous composition comprising (i) a factor VII polypeptide in a concentration of from about 0.1 mg/ml to about 10 mg/ml, (ii) an agent suitable for keeping pH in the range of from about 5.5 to about 7.0 is selected from the group consisting of acids and salts in a concentration of about 1 mM to about

50 mM, (iii) an agent selected from a calcium salt, a magnesium salt, or a mixture thereof, wherein the concentration of (iii) is at least 20 mM, (iv) an ionic strength modifying agent, sodium chloride (at least about 5 mM), (v) a tonicity modifying agent in a concentration from 1 mM to 500 mM, (vi) a non-ionic surfactant is a polysorbate or a poloxamer or a polyethylene alkyl ether, further comprising factor VII polypeptide is stable for at least 6 months at 2-8°C and recombinant human factor VIIa. Furthermore, the claims are further comprised of (vii) an antioxidant in a concentration of from about 0.1 to about 5.0 mg/ml. Furthermore, claim 24 is drawn to a composition further comprising (viii) a preservative.

10. Johannessen et al disclose factor VIIa for the manufacture of a medicament for treatment of a condition affectable by Factor VIIa, medicament being for subcutaneous, intra-muscular or intradermal administration...shows a prolonged biological half-life (see abstract). Furthermore, the reference discloses that the Factor VII a variants have substantially the same or improved biological activity relative to wild-type Factor VIIa...at least about 25%, preferably at least 50%, more preferably at least about 75% and most preferably at least about 90% of the specific activity of Factor VII a that has been produced in the same cell type (see p. 4, lines 33-36). Furthermore, the reference discloses that the medicament can also be stable aqueous solution ready for administration...the FVIIa activity in the formulation is preferably from about 0.1 mg/ml to about 50 mg/ml...about 0.6 mg/ml to about 25 mg/ml...about 3 mg/ml to about 15 mg/ml (see p. 9, lines 15-21). Additionally, the reference discloses that the medicament may also comprise salt in order to give an isotonic solution, e.g. NaCl, KCl...in an

amount of more than 1.0 mg/ml (see p. 9, lines 22-24). Calcium, or other divalent metal ions, is necessary for the maintenance of the FVIIa activity...calcium chloride...in an amount of more than 0.15 mg/ml (see p. 9, lines 25-28). Therefore, this reads on claims 1 and 7. Further, the reference discloses that an amino acid is preferably used to buffer the system and it also protects the protein if the formulation is freeze-dried ...a suitable buffer could be glycine, lysine, arginine, histidine or glycylglycine (see p. 9, lines 29-31). Further, the reference discloses that a non-ionic surfactant may also be present in the medicament...block-copolymers, such as poloxamer, or polyoxyethylene sorbitan fatty acid ester...at least in a concentration of at least 0.01 mg/ml (see p. 9, lines 32-36). Furthermore, the reference discloses that mono- or disaccharides, polysaccharides such as low molecular weight dextrins, or sugar alcohols (sorbitol, glycerol or mannitol) may be added...also may comprise antioxidants such as bisulfite...methionine...preservatives such as benzyl alcohol, phenol, sorbic acid, parabens, and chlorocresol may be added...the pH of the preparation is preferably adjusted to a value in the interval of 2-9...having a pH from about 5.0 to about 7.5 are preferred (see p. 10, lines 1-14). This meets the limitation of claim 24. Thus, the prior art meets the limitation of claims 1-7, 9-19, 21-26, 29-31.

Rejection-35 U.S.C. 103

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

12. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

13. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

14. Claim 8 is rejected under 35 U.S.C. 103(a) as being unpatentable over The Medicine Catalogue (Laegemiddel Kataloget) as applied to claims 1-7, 9-16, 21-23, 25-26 and 29-31 above, and further in view of Miekka et al (WO 97/19687).

15. The instant claim is drawn to a liquid, aqueous composition comprising (i) a factor VII polypeptide in a concentration of from about 0.1 mg/ml to about 10 mg/ml, (ii) an agent suitable for keeping pH in the range of from about 5.5 to about 7.0 is selected from the group consisting of acids and salts in a concentration of about 1 mM to about

50 mM, (iii) an agent selected from a calcium salt, a magnesium salt, or a mixture thereof, wherein the concentration of (iii) is at least 20 mM, wherein the magnesium salt is selected from the group consisting of magnesium chloride, magnesium acetate, magnesium sulphate, magnesium gluconate and magnesium laevulate, further comprising factor VII polypeptide is stable for at least 6 months at 2-8°C and recombinant human factor VIIa.

16. As described supra, The Medicine Catalogue discloses a composition with recombinant coagulation factor VIIa, with 105 mg calcium chloride, 1.3 mg glycylglycine, 30 mg mannitol, 3.0 mg sodium chloride and 0.1 mg polysorbate per 80 ml, wherein the composition has a pH of 5.4 to 6.0 (see Dispensed in the form of). When a simple calculation is performed for $CaCl_2$ concentration using 105 mg and molecular weight of 111 g/mol and dissolving in 2, 4 and 8mls of sterile water, the $CaCl_2$ concentrations are 118 mM, 236 mM and 473 mM, respectively for 8, 4 and 2mls. For sodium chloride (MW 59 g/mol) and using 3 mg and dissolving in 2, 4 and 8mls of sterile water, the sodium chloride concentrations are 6, 12 and 24 mM, respectively for 8, 4 and 2mls (see Suggested dosage). This meets the limitation of at least 20 mM of calcium salt of claim 1 (iii) and at least 5 mM of sodium chloride. Therefore, this reads on claim 1-7, 9-16, 21-23 and 26. With regards to factor VII polypeptide stable for at least 6 months at 2-8C, the stability of the composition is a property of its components, accordingly, since the prior art composition has the same components as the composition of instant claims, the stability will be the same. Thus, this reads on claim 25. The Medicine Catalogue further teaches that factor VII polypeptide concentration is 0.6 mg/ml when a calculation

is performed using the amount of recombinant coagulation factor (1.2 mg, 2.4 mg or 4.8 mg) is dissolved in 2 ml, 4 ml, and 8 ml of sterile water (see Suggested dosage under "Preparation of injection fluid"). This reads on claim 29. Furthermore, The Medicine Catalogue teaches that the preparations are dissolved in varying amounts of sterile water, and that they are administered by a bolus injection (see Suggested dosage). This reads on claims 30-31. Additionally, since different amounts of sterile water are used to reconstitute the composition while the mass of the excipients does not change, the concentrations of the excipients will be commensurate with instant claims. For example, 30 mg of mannitol (MW 182.17 g/mol) used in The Medicine Catalogue, which meets the limitation of claim 11 is found to be 82 mM for 2ml, 41 mM for 4ml and 21 mM for 8mls of sterile water, meeting the limitations of claims 12-13. Therefore, The Medicine Catalogue meets the limitations of claims 1-7, 9-16, 21-23, 25-26 and 29-31. The difference between the reference and the instant claims is that the reference does not teach magnesium salt, and the antioxidant (L-methionine) in the concentration of about 0.1 to about 5.0 mg/ml.

17. However, Miekka et al teach the preparation of liquid formulation of plasma proteins, particularly blood coagulation factors (see abstract). Furthermore, the reference teaches that calcium, magnesium and manganese are equivalent divalent metal ions in the art of protein stabilization (see p. 23, lines 11-21).

18. Therefore it would have been obvious for one of ordinary skill in the art to combine the teachings of The Medicine Catalogue and substitute the calcium salt with magnesium salts. There is a reasonable expectation of success since the art recognizes

that calcium, magnesium and manganese are equivalent divalent metal ions in the art of protein stabilization. One of ordinary skill in the art would be motivated to substitute one metal for the other, since calcium, magnesium and manganese are equivalent divalent metal ions.

Double Patenting

19. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

20. Claims 1, 7, 8, 10-12, 14-15, 17-19 and 24 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-7, 11, 12 and 16-19 of copending Application No. 10/602340. Although the conflicting claims are not identical, they are not patentably distinct from each other because the copending claims differ from instant claims only in that instant independent

claim 1 recites a minimum concentration of the salt, whereas the copending independent claim 1 is silent on the concentration. However, copending claim 16 recites a range of concentrations of the salt, which substantially overlaps the concentration limitations of instant claim 1. Furthermore, claim 1 of copending application recites an antioxidant that is not recited in the instant claim 1. However, in the instant application, claims16-19 recite antioxidant limitations. Thus, if one practiced the claims of the copending application, one would necessarily lead to the instant claimed invention.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

21. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Julie Ha whose telephone number is 571-272-5982. The examiner can normally be reached on Mon-Fri, 8:00 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on 571-272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Julie Ha
Patent Examiner
AU 1654

5/24/07
ANISH GUPTA
PRIMARY EXAMINER